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Left Ventricular Systolic Function in Patients with Systemic Lupus Erythematosus and Its Association with Cardiovascular Events



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Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with potential cardiovascular involvement. The aim of this study was to assess left ventricular (LV) systolic function in a large cohort of patients with SLE using standard echocardiographic measurements and global longitudinal strain (GLS) by two-dimensional speckle-tracking analysis. Furthermore, the association between echocardiographic parameters and the occurrence of cardiovascular events was assessed.

Methods: A total of 102 patients with SLE (88% women; mean age, 43 ± 14 years) undergoing a dedicated multidisciplinary assessment were analyzed, including echocardiography, at the time of their first visit. A control group consisted of 50 age- and sex-matched healthy subjects.

Results: Compared with control subjects, patients with SLE showed impaired LV systolic function on the basis of LV ejection fraction ($51 \pm 6\%$ vs $62 \pm 6\%$, $P < .001$) and by LV GLS ($-15 \pm 3\%$ vs $-19 \pm 2\%$, $P < .001$). During a median follow-up period of 2 years (interquartile range, 1–6 years), 38 patients (37%) developed cardiovascular events. Kaplan-Meier survival curves showed that patients with SLE with more impaired LV GLS (on the basis of the median value of -15%) experienced higher cumulative rates of cardiovascular events compared with those with less impaired LV GLS ($\chi^2 = 8.292$, log-rank $P = .004$). On multivariate Cox regression analysis, LV GLS demonstrated an independent association with cardiovascular events (hazard ratio, 2.171; 95% CI, 1.015–4.642; $P = .046$), whereas LV ejection fraction was not significantly associated with the outcome.

Conclusions: In patients with SLE, LV systolic function as measured by LV GLS is significantly impaired and associated with cardiovascular events, potentially representing a new tool to improve risk stratification in these patients. (J Am Soc Echocardiogr 2020;33:1116–22.)

Keywords: Left ventricular function, global longitudinal strain, systemic lupus erythematosus, cardiovascular outcome

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that may involve the cardiovascular system and is associated with high cardiovascular morbidity and mortality.^{1,2} Diagnosis of myocardial involvement, particularly at an early stage, represents still a challenge because symptoms in patients with SLE are often nonspecific, and myocardial involvement may be present even without symptoms. Current diagnostic tools, namely echocardiography, may be limited by low sensitivity to detect myocardial dysfunction, leading to underestimation of cardiac involvement in these patients. The use of advanced echocardiographic techniques, in particular speckle-tracking echocardiography (STE), is currently proposed as a more sensitive and reproducible approach to detect subtle myocardial systolic dysfunction compared with conventional echocardiographic measures such as left ventricular ejection fraction (LVEF).^{3,4} Using this imaging technique, left ventricular (LV) global longitudinal strain (GLS) can be measured, and this parameter has been shown to be clinically useful for early detection of myocardial dysfunction and risk stratification in several cardiovascular diseases, including cardiac involvement in autoimmune disorders such as systemic sclerosis.⁵

However, only small studies have assessed the diagnostic value of LV GLS for myocardial involvement in patients with SLE,^{6,7} and so far no

Abbreviations
CAD = Coronary artery disease
CVA = Cerebrovascular accident
GLS = Global longitudinal strain
HR = Hazard ratio
LV = Left ventricular
LVEF = Left ventricular ejection fraction
SLE = Systemic lupus erythematosus
SLEDAI = Systemic lupus erythematosus disease activity index
STE = Speckle-tracking echocardiography

data have been published on the potential prognostic value of this measure. The purpose of the present study was therefore to assess LV systolic function in a large cohort of patients with SLE using standard and advanced echocardiographic measurements, including LV GLS; in particular, the association between LV GLS and development of cardiovascular events was explored.

METHODS

Patient Population

Patients referred to the Department of Rheumatology at Leiden University Medical Center for an extensive multidisciplinary assessment between May 2007 and December 2017, and

who underwent echocardiographic analysis, were included in the present study.⁸ Patients fulfilled the 1997 American College of Rheumatology and 2012 Systemic Lupus Erythematosus International Collaborating Clinics classification criteria for SLE.^{9,10} The indication to perform echocardiography was one or more of the following: (1) potential cardiovascular symptoms (chest discomfort, dyspnea, and palpitations); (2) suspected endocarditis (cardiac murmur and other signs of endocarditis); and (3) assessment of cardiac source of embolism in case of recent cerebrovascular accident (CVA; Table 1). Diagnosis of endocarditis, pericarditis, and valvular disease was confirmed by baseline echocardiography (Table 2).

For each patient, the earliest accessible echocardiographic examination performed during the multidisciplinary assessment was analyzed. When included in the multidisciplinary assessment, all patients gave informed consent for the use of clinically collected data.

A control group was identified from the echocardiography database having structural normal hearts and consisted of 50 age- and sex-matched healthy subjects.

Clinical Data

At inclusion, data on age, sex, duration of SLE, SLE characteristics, cardiovascular disease-related risk factors (smoking, hypertension, diabetes, dyslipidemia), comorbidities, and body mass index were recorded. Specific disease-related characteristics at baseline were also reported, including diagnosis of neuropsychiatric SLE, SLE disease activity index (SLEDAI) and Systemic Lupus Erythematosus International Collaborating Clinics 2012 classification criteria for SLE, positive antinuclear antibody, antiphospholipid antibodies, anti-double-stranded deoxyribonucleic acid, anti-Smith antibodies, elevated C-reactive protein, and reduced creatinine clearance.

Patients were followed from the baseline echocardiographic examination on for the development of cardiovascular events, which were defined as CVA, pulmonary embolism, coronary artery disease (CAD) requiring revascularization, hospitalization for heart failure, and development of sustained ventricular and/or supraventricular arrhythmias. The time till cardiovascular events was calculated from the date of echocardiography (close to the confirmed diagnosis of SLE).

Table 1 Baseline clinical characteristics of patients with SLE (N = 102)

Clinical characteristics	Value
Age, y	43 ± 14
Sex, female	90 (88)
Duration of SLE, y	13 ± 9
Systolic blood pressure, mm Hg	123 ± 17
Diastolic blood pressure, mm Hg	74 ± 10
Cardiovascular disease-related factors	
Hypertension	32 (31)
BMI, kg/m ²	24 ± 5
BMI > 25 kg/m ²	35 (34)
Smoking	25 (24)
Coronary artery disease	1 (1)
History of pulmonary embolism	2 (2)
History of CVA	4 (4)
Previous heart failure	0 (0)
Diabetes mellitus	4 (4)
Hypercholesterolemia	33 (32)
SLE-related factors	
Creatinine clearance, mL/min	68 ± 37
NPSLE	43 (42)
SLEDAI score	9 ± 8
SLICC score	0.9 ± 1
Positive antiphospholipid antibodies	35 (34)
Positive antinuclear antibody	102 (100)
Positive anti-double-stranded DNA	59 (58)
Positive anti-Smith antibodies	14 (14)
C-reactive protein, mg/L	12 ± 30
Medications	
Prednisolone	51 (50)
Azathioprine	24 (24)
Hydroxychloroquine	45 (44)
Cardiovascular medications	
ACE inhibitors/ARBs	18 (18)
β-blockers	9 (9)
Diuretics	9 (9)
Calcium channel blockers	9 (9)
Vitamin K antagonists or NOACs	12 (12)

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; DNA, deoxyribonucleic acid; NOAC, novel oral anticoagulant; NPSLE, neuropsychiatric SLE; SLICC, Systemic Lupus Erythematosus International Collaborating Clinics.

Echocardiography

Commercially available ultrasound systems equipped with M55 transducers (Vivid 7 or E9, GE Vingmed Ultrasound, Horten, Norway) were used to acquire two-dimensional, color, continuous, and pulsed-wave Doppler data from the parasternal and apical views with the patient in the left lateral decubitus position. Images were stored digitally on hard disks for offline analysis (EchoPAC version 202; GE Medical Systems, Milwaukee, WI). LV end-diastolic and

HIGHLIGHTS

- In SLE patients, LV systolic function as measured by LV GLS is significantly impaired.
- Impaired LV GLS in SLE patients is associated with cardiovascular events.
- Assessment of LV GLS may significantly improve risk-stratification in SLE patients.

end-systolic volumes were measured from the apical two- and four-chamber views using the Simpson method, and LVEF was derived.¹¹ LV mass was calculated and defined according to current recommendations and guidelines.¹¹ Left atrial volume was calculated using the Simpson method and indexed to body surface area.¹¹

Transmitral inflow pattern was measured using pulsed-wave Doppler (E wave), and Doppler tissue imaging was applied at the septal and lateral mitral annulus during early diastole (average e' and E/e' ratio). LV diastolic function was considered normal if more than half of the following variables did not meet the cutoff values for identifying abnormal function: annular septal e' velocity < 7 cm/sec, annular lateral e' velocity < 10 cm/sec, average E/e' ratio

> 14 , left atrial maximum volume index > 34 mL/m², and peak tricuspid regurgitation velocity > 2.8 m/sec. LV diastolic dysfunction was defined when more than half of the available parameters met the aforementioned cutoff values. LV diastolic function was indeterminate if half of the parameters did not meet these cutoff values.¹²

Systolic pulmonary artery pressure was estimated by determining right ventricular systolic pressure, calculated from the tricuspid regurgitation peak gradient, and adding right atrial pressure estimated by the inferior vena cava diameter and degree of respiratory collapse according to current recommendations.¹³

Two-Dimensional Speckle-Tracking Strain Echocardiography

LV GLS was measured on two-dimensional STE using commercially available software (EchoPAC version 202).¹⁴ In the apical three-, four-, and two-chamber views, the LV endocardial border was traced, and the software displayed a region of interest automatically encompassing the LV myocardial wall; if needed, the region of interest was adjusted manually. LV GLS was then calculated as the average of longitudinal strain values of each apical view, and a color-coded 17-segment bull's-eye plot was provided (Figure 1).

Statistical Analysis

Continuous variables are presented as mean \pm SD if normally distributed or as median and interquartile range otherwise. Categorical variables are presented as frequencies and percentages. Patients with SLE were compared with 50 healthy control subjects, matched for age and sex, using the independent-samples t test. One-way analysis of variance and the Mann-Whitney test were used for normally distributed and skewed variables, respectively, whereas the χ^2 test was used to compare categorical variables. Cumulative event rates were analyzed on the basis of the Kaplan-Meier survival method for patients divided into two groups on the basis of median LV GLS value (-15%) and compared using the log-rank test. The association between LV GLS and cardiovascular events was evaluated using uni- and multivariate Cox regression analyses. The level of significance for variables to be included in the multivariable analysis was set at $P < .05$, but other clinically crucial variables (such as sex) were also included in the multivariate model. Hazard ratios (HRs) and 95% CIs are presented.

Statistical analysis was performed using SPSS for Windows version 23.0 (IBM, Armonk, NY). A two-tailed P value $< .05$ was considered to indicate statistical significance.

RESULTS

Baseline Clinical Characteristics

A total of 102 patients with SLE (88% women; mean age, 43 ± 14 years) were included in this analysis. Clinical characteristics of the overall population are presented in Table 1. All patients had neuropsychiatric symptoms, but after the extensive multidisciplinary assessment, only 43 patients (42%) were diagnosed with neuropsychiatric SLE. Mean SLEDAI was relatively high in the overall cohort. The prevalence of comorbidities was as follows: 32 of patients with SLE (31%) had hypertension (any grade), one (1%) had previously diagnosed CAD, four (4%) had diabetes mellitus, and 33 (32%) had hypercholesterolemia. The presence of antiphospholipid antibodies was observed in 35 patients (34%).

Table 2 Baseline echocardiographic characteristics in patients with SLE compared with healthy control subjects

Echocardiographic characteristic	SLE group (n = 102)	Healthy control subjects (n = 50)	P
LV mass, g	141 \pm 57	130 \pm 35	.159
LVEDV, mL	93 \pm 33	108 \pm 31	.005
LVEF, %	51 \pm 6	62 \pm 6	<.001
LVEF \leq 50%	46 (45)	0	<.001
LV GLS, %	-15 \pm 3	-19 \pm 2	<.001
e' lateral, cm/sec	12 \pm 3	12 \pm 3	.587
e' septal, cm/sec	9 \pm 2	10 \pm 2	.014
e' average, cm/sec	10 \pm 3	11 \pm 3	.272
E/e' ratio	8 (6–10)	7 (6–8)	.001
E/A ratio	1.1 (0.9–1.4)	1.1 (0.9–1.3)	.752
E, cm/sec	82 (68–99)	70 (60–82)	.010
LAVI, mL/m ²	26 \pm 9	23 \pm 6	.112
sPAP, mm Hg	20 (15–26)	17 (9–22)	<.001
LV diastolic dysfunction	4 (4)	0	.154
LV diastolic function indeterminate	9 (9)	0	.029
Moderate to severe VHD	33 (32)	0	<.001
Libman-Sacks endocarditis	2 (2)	0	.319
Pericarditis	7 (7)	0	.055
PFO	5 (5)	0	.111

LAVI, Left atrial volume index; LVEDV, LV end-diastolic volume; PFO, patent foramen ovale; sPAP, systolic pulmonary artery pressure; VHD, valvular heart disease.

Bold values represent $P < 0.05$.

Data are expressed as mean \pm SD, as number (percentage), or as median (interquartile range).

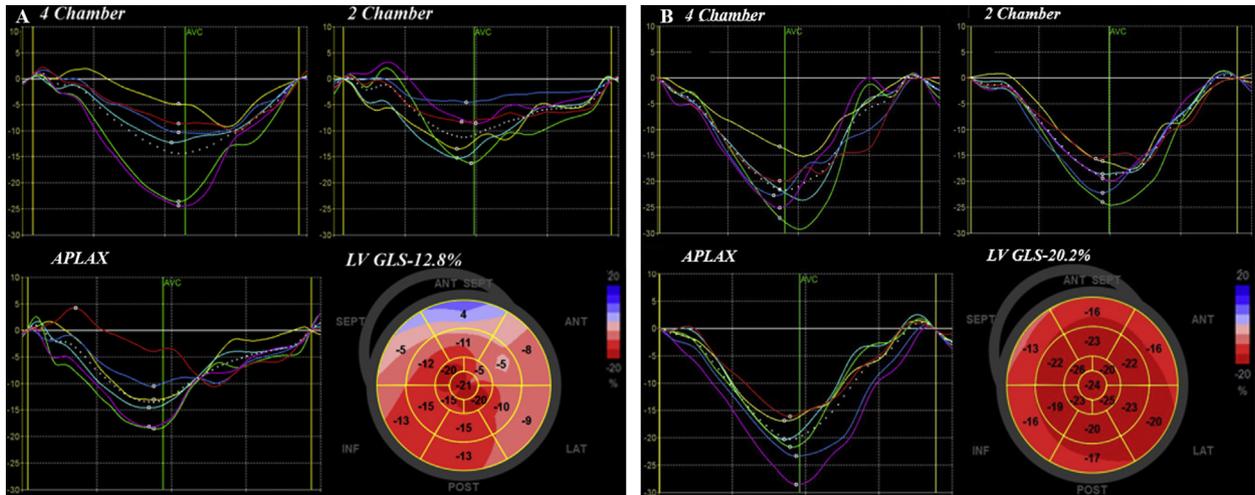


Figure 1 Example of assessment of LV GLS by speckle-tracking strain echocardiography in patients with SLE (**A**; LV GLS = -12.8%) compared with a healthy individual (**B**; LV GLS = -20.2%) displayed with color-coded bull's-eye plots for longitudinal strain. Curves of longitudinal strain per segment and averaged among the segments (*dotted line* for the three-chamber, four-chamber, and two-chamber apical views) are also displayed. *APLAX*, Apical long-axis.

Baseline Echocardiographic Characteristics

Baseline echocardiographic characteristics of the overall population are presented in [Table 2](#). When comparing echocardiographic measures between patients with SLE and age- and sex-matched healthy control subjects, patients with SLE showed significantly lower LVEFs ($51 \pm 6\%$ vs $62 \pm 6\%$, $P < .001$) compared with healthy control subjects ([Table 2](#)). Although no patients with SLE were known to have heart failure symptoms, 46 of patients with SLE (45%) had slightly impaired LVEFs ($\leq 50\%$). Importantly, LV GLS was also significantly decreased in patients with SLE compared with healthy control subjects (median, $-15 \pm 3\%$ vs $-19 \pm 2\%$; $P < .001$). As both measures of LV systolic function, LVEF and LV GLS showed a significant correlation ($r = 0.679$, $P < .001$); however, a larger percentage of patients (89% [91 patients]) showed impaired LV GLS on the basis of the lower cutoff of normality proposed by current recommendations (-18%),¹⁵ and therefore 50% of patients with preserved LVEFs showed impaired LV GLS.

When assessing LV diastolic function, we observed that the prevalence of LV diastolic dysfunction was not very high ([Table 2](#)), at 4% in the overall population and 9% indeterminate.

Associations between Echocardiographic Characteristics and Cardiovascular Events

During a median follow-up period of 2 years (interquartile range, 1–6 years), 38 patients (37%) developed cardiovascular events: 14 (14%) developed CVAs, 14 (14%) arrhythmias, five (5%) CAD requiring revascularization, and four (4%) pulmonary embolism, and four (4%) were hospitalized for heart failure ([Figure 2](#)).

Kaplan-Meier survival curves show that patients with SLE with more impaired LV GLS (on the basis of the median value of -15%) experienced higher cumulative rates of cardiovascular events compared with patients with less impaired LV GLS ($\leq -15\%$; $\chi^2 = 8.292$, log-rank $P = .004$; [Figure 3](#)). At 4-year follow-up, 18% of patients with SLE with less impaired LV GLS ($\leq -15\%$) developed cardiovascular events compared with 47% with more impaired LV GLS ($> -15\%$).

In multivariate Cox regression models ([Table 3](#)), LV GLS demonstrated a significant and independent association with cardiovascular events (HR, 2.171; 95% CI, 1.05–4.642; $P = .046$), together with age (HR, 1.044; 95% CI, 1.018–1.070; $P = .001$); conversely, LVEF was not significantly associated with cardiovascular events (HR, 0.963;

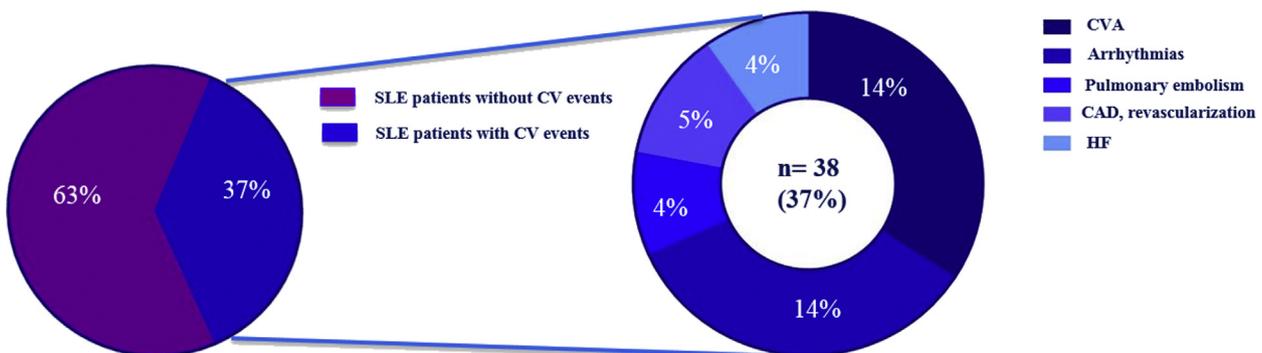


Figure 2 Prevalence of cardiovascular events during follow-up in patients with SLE. *HF*, Heart failure.

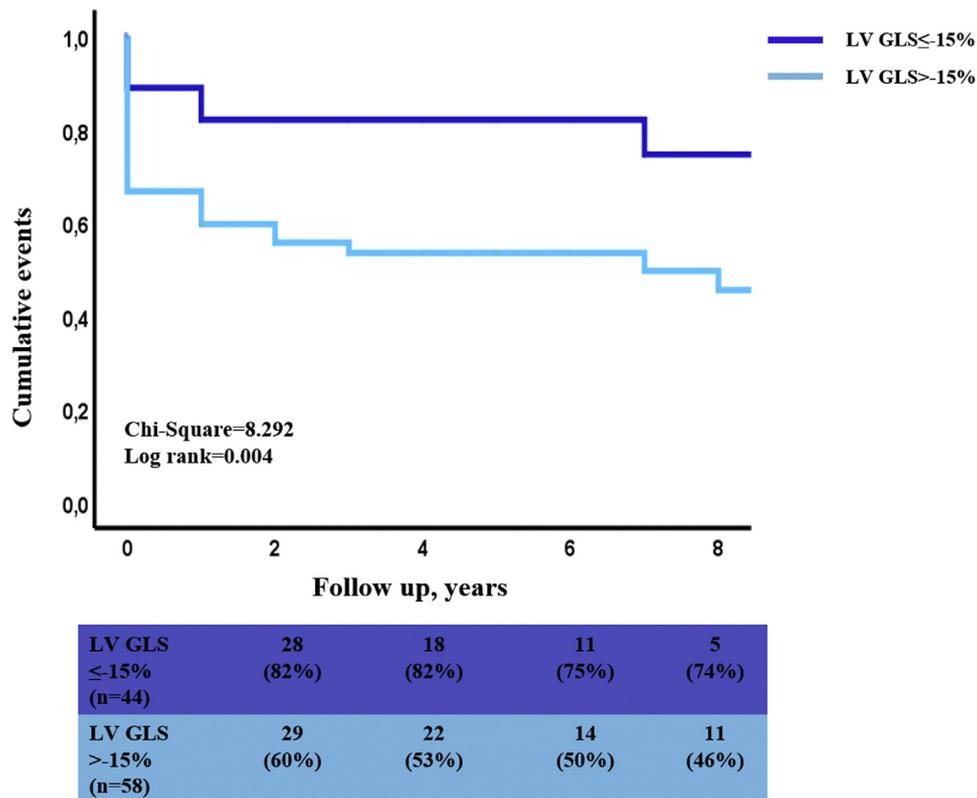


Figure 3 Kaplan-Meier curves showing the association of LV GLS (dichotomized according to median value of -15%) with the development of cardiovascular events.

95% CI, 0.915–1.014; $P = .156$) in the SLE population (Table 3), nor the parameters of LV diastolic function (Table 3).

Importantly, there was no significant association between the severity of disease (based, for example, on the SLEDAI or on the diagnosis of neuropsychiatric SLE) and cardiovascular events.

DISCUSSION

The main findings of the present study can be summarized as follows: (1) in patients with SLE, LV systolic dysfunction was relatively frequent, and LV GLS in particular was significantly impaired compared with healthy control subjects, and (2) in these patients, impaired LV GLS was independently associated with the occurrence of cardiovascular events, whereas standard echocardiographic parameters were not.

LV Systolic Dysfunction in Patients with SLE

In patients with SLE, the long-term inflammatory burden and the immune system abnormalities can result in several forms of cardiovascular involvement, including valvular heart disease, myocarditis, myocardial fibrosis, pericarditis, inflammatory, and atherosclerotic and thromboembolic changes in the vascular system, leading to early CAD, congestive heart failure, electrical disturbances leading to arrhythmias and conduction abnormalities, pulmonary embolism, and CVAs.^{1,16-18} However, myocardial involvement at early stage of SLE is still largely underdiagnosed, because of the subtle clinical manifestations and the limitations of current diagnostic tools.

Studies based on autopsy have shown myocardial involvement in 40% to 50% of patients with SLE,^{16,19} while only 7% to 10% of patients with SLE are clinically diagnosed with myocardial injury.²⁰ In the present study, a large cohort of patients with SLE was studied using standard and advanced echocardiographic measures. Of note, 43 patients (42%) were diagnosed with neuropsychiatric SLE. In this regard, the true prevalence of neuropsychiatric SLE is unknown, but earlier studies suggest that it may affect 12% to 80% of patients with SLE²¹⁻²⁴ and that it is a major source of morbidity and mortality.^{21,24} In this population, when using conventional parameters of LV systolic function such as LVEF, a relatively high percentage of patients (45%) showed mild LV systolic dysfunction, although with a low prevalence of comorbidities such as diabetes and CAD and without heart failure symptoms. Furthermore, when assessing LV function with a more sensitive tool such as LV GLS, the mean value was significantly lower ($-15 \pm 3\%$) than in healthy subjects (control group) and in a large percentage of patients was substantially impaired according to the normal values (-18% to -21%) proposed by current recommendations.¹⁵ These findings therefore suggest primary myocardial involvement due to SLE, but still at a subclinical level. Previous studies have also explored the prevalence of LV systolic dysfunction in patients with SLE, and when using the reduction of systolic function in standard echocardiographic parameters such as LVEF, it varied from 16% to 45%.²⁴⁻²⁶ Initial studies have also shown an impairment of LV GLS in patients with SLE. Buss *et al.*⁶ showed, in 67 young patients with SLE, significant impairment in LV GLS compared with healthy control subjects, and similar results were obtained by Huang *et al.*⁷ in 34 consecutive patients with SLE.

Table 3 Cox regression uni- and multivariate analyses for the occurrence of cardiovascular events in the patients with SLE

Clinical or echocardiographic parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.047 (1.022–1.072)	<.001	1.044 (1.018–1.070)	.001
Sex, female	2.493 (0.599–10.372)	.209	2.529 (0.608–10.518)	.202
SBP	1.014 (0.994–1.034)	.164		
Hypertension	1.350 (0.671–2.717)	.400		
Diabetes mellitus	2.580 (0.788–8.448)	.117		
Hypercholesterolemia	0.529 (0.231–1.209)	.131		
Creatinine clearance	1.002 (0.993–1.012)	.599		
NPSLE	1.254 (0.662–2.375)	.488		
SLEDAI	0.998 (0.959–1.038)	.912		
Antiphospholipid antibodies	0.964 (0.483–1.923)	.918		
LVEF	0.963 (0.915–1.014)	.156		
LVEDV	1.001 (0.992–1.011)	.818		
Average E/e' ratio	1.098 (0.997–1.208)	.057		
e' septal < 7 cm/sec	1.884 (0.889–3.991)	.098		
LAVI	1.017 (0.986–1.049)	.282		
LV diastolic dysfunction	2.608 (0.794–8.564)	.114		
sPAP	1.026 (0.999–1.053)	.059		
LV GLS (median value, –15%)	2.640 (1.246–5.591)	.011	2.171 (1.015–4.642)	.046

LAVI, Left atrial volume index; LVEDV, LV end-diastolic volume; NPSLE, neuropsychiatric SLE; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure.

Clinical and Echocardiographic Associates of Cardiovascular Events in SLE

Cardiovascular complications are among the most common causes of death in patients with SLE.^{1,2} Although several studies have identified clinical prognostic factors in patients with SLE, few of them focused on cardiovascular events, and no studies so far have explored the prognostic value of advanced echocardiographic measures such as LV GLS. According to the literature, the occurrence of cardiovascular events varies from 25% to 55% in SLE and neuropsychiatric SLE groups.^{17,18} In the present study, a high incidence of cardiovascular events (37%) was observed.

The mechanism behind the occurrence of cardiovascular events in patients with SLE is largely unknown and probably multifactorial, including disease-specific factors; however, systematic reviews and meta-analyses demonstrated that the activity and severity of the disease, expressed namely by the systemic SLE damage and SLEDAI scores, as well as disease duration, have a small prognostic impact on cardiovascular events.^{17,27,28} The limited prognostic value of the SLEDAI score also observed in our study might be explained by the fact that some important alterations, such as myositis, hemolytic anemia, and cardiopulmonary and gastrointestinal manifestations, are not considered, and the score therefore does not capture the severity of the disease within an organ system. Also, although the prevalence of hypertension (any stage) and positive antiphospholipid antibodies (not antiphospholipid syndrome) was remarkable in our study population, these variables did not show significant associations with cardiovascular events (Table 3).

In the present study, when exploring the association between echocardiographic parameters and the occurrence of cardiovascular events, only LV GLS was significantly associated with the outcome, independent of age and sex; in particular, LVEF and LV diastolic function were not significantly associated with outcome. LV GLS may be therefore able to reflect not only primary (subclinical) myocardial involvement but also an overall increased risk for cardiovascular events with different mechanisms (including autoimmune inflammation, specifically at a vascular level, increased antiphospholipid antibodies, etc.). Even in the presence of nearly “normal” LVEF, micro- and macrovascular abnormalities might affect LV GLS and can lead to CVA, arrhythmias, and other cardiovascular events. Recently, the association of subclinical LV myocardial dysfunction by GLS and incident atrial fibrillation was reported in patients with ischemic stroke.²⁹ In a community-based cohort study in patients free of cardiovascular disease, GLS was associated with silent brain infarcts and white matter hyperintensities, both features of small-vessel disease.³⁰

LV GLS could be therefore considered as a new tool to diagnose subclinical myocardial involvement and to optimize individual patient management and risk stratification.

Study Limitations

Several limitations should be acknowledged. In the present study, 42% of the patients had diagnosis of neuropsychiatric SLE; therefore, the results cannot be applied to an SLE population with a lower prevalence of neuropsychiatric SLE. Potential bias could be also present

because patients were selected on the basis of the availability of two-dimensional transthoracic echocardiographic findings. Because of the small number of cardiovascular events, multivariate analysis was performed including a limited number of variables; however, all statistically or clinically relevant parameters could be included. Further studies with larger populations, in a multicenter setting, should confirm these results.

CONCLUSION

In patients with SLE, LV systolic function as measured by LV GLS is significantly impaired, compared to healthy control subjects, and is associated with cardiovascular events. Implementation of LV GLS in the early assessment of these patients may significantly improve their risk stratification.

REFERENCES

1. Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:338-46.
2. Abu-Shakra M, Gladman DD, Urowitz MB. Mortality studies in SLE: how far can we improve survival of patients with SLE. *Autoimmun Rev* 2004;3:418-20.
3. Marwick TH, Shah SJ, Thomas JD. Myocardial strain in the assessment of patients with heart failure: a review. *JAMA Cardiol* 2019;4:287-94.
4. Tops LF, Delgado V, Marsan NA, Bax JJ. Myocardial strain to detect subtle left ventricular systolic dysfunction. *Eur J Heart Fail* 2017;19:307-13.
5. van Wijngaarden SE, Ben Said-Bouyeri S, Ninaber MK, Huizinga TWJ, Schaliq MJ, Bax JJ, et al. Progression of left ventricular myocardial dysfunction in systemic sclerosis: a speckle-tracking strain echocardiography study. *J Rheumatol* 2019;46:405-15.
6. Buss SJ, Wolf D, Korosoglou G, Max R, Weiss CS, Fischer C, et al. Myocardial left ventricular dysfunction in patients with systemic lupus erythematosus: new insights from tissue Doppler and strain imaging. *J Rheumatol* 2010;37:79-86.
7. Huang BT, Yao HM, Huang H. Left ventricular remodeling and dysfunction in systemic lupus erythematosus: a three-dimensional speckle tracking study. *Echocardiography* 2014;31:1085-94.
8. Magro-Checa C, Kumar S, Ramiro S, Beart-van de Voorde LJ, Eikenboom J, Ronen I, et al. Are serum autoantibodies associated with brain changes in systemic lupus erythematosus? MRI data from the Leiden NP-SLE cohort. *Lupus* 2019;28:94-103.
9. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
10. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677-86.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-70.
12. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;17:1321-60.
13. Pyxaras SA, Pinamonti B, Barbati G, Santangelo S, Valentincic M, Cettolo F, et al. Echocardiographic evaluation of systolic and mean pulmonary artery pressure in the follow-up of patients with pulmonary hypertension. *Eur J Echocardiogr* 2011;12:696-701.
14. Vollema EM, Sugimoto T, Shen M, Tastet L, Ng ACT, Abou R, et al. Association of left ventricular global longitudinal strain with asymptomatic severe aortic stenosis: natural course and prognostic value. *JAMA Cardiol* 2018;3:839-47.
15. Ajmone Marsan N, Michalski B, Cameli M, Podlesnikar T, Manka R, Sitges M, et al. EACVI survey on standardization of cardiac chambers quantification by transthoracic echocardiography. *Eur Heart J Cardiovasc Imaging* 2020;21:119-23.
16. Knockaert DC. Cardiac involvement in systemic inflammatory diseases. *Eur Heart J* 2007;28:1797-804.
17. Ballocca F, D'Ascenzo F, Moretti C, Omede P, Cerrato E, Barbero U, et al. Predictors of cardiovascular events in patients with systemic lupus erythematosus (SLE): a systematic review and meta-analysis. *Eur J Prev Cardiol* 2015;22:1435-41.
18. Roldan CA, Gelgand EA, Qualls CR, Sibbitt WL Jr. Valvular heart disease by transthoracic echocardiography is associated with focal brain injury and central neuropsychiatric systemic lupus erythematosus. *Cardiology* 2007;108:331-7.
19. Vivero F, Gonzalez-Echavarrri C, Ruiz-Estevéz B, Maderuelo I, Ruiz-Iratorza G. Prevalence and predictors of valvular heart disease in patients with systemic lupus erythematosus. *Autoimmun Rev* 2016;15:1134-40.
20. Doria A, Iaccarino L, Sarzi-Puttini P, Atzeni F, Turriel M, Petri M. Cardiac involvement in systemic lupus erythematosus. *Lupus* 2005;14:683-6.
21. Schwartz N, Stock AD, Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. *Nat Rev Rheumatol* 2019;15:137-52.
22. Unterman A, Nolte JE, Boaz M, Abady M, Shoenfeld Y, Zandman-Goddard G. Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. *Semin Arthritis Rheum* 2011;41:1-11.
23. Borowoy AM, Pope JE, Silverman E, Fortin PR, Pineau C, Smith CD, et al. Neuropsychiatric lupus: the prevalence and autoantibody associations depend on the definition: results from the 1000 faces of lupus cohort. *Semin Arthritis Rheum* 2012;42:179-85.
24. Li X, Xiang X, Sun J, Liu S, Liu Y, Feng L, et al. Prevalence, outcome and prognostic factors of neuropsychiatric systemic lupus erythematosus: a real world single center study. *Mod Rheumatol* 2019;30:321-6.
25. de Godoy MF, de Oliveira CM, Fabri VA, de Abreu LC, Valenti VE, Pires AC, et al. Long-term cardiac changes in patients with systemic lupus erythematosus. *BMC Res Notes* 2013;6:171.
26. Mohammed AG, Alghamdi AA, MA AL, Al-Homood IA. Echocardiographic findings in asymptomatic systemic lupus erythematosus patients. *Clin Rheumatol* 2017;36:563-8.
27. Afeltra A, Vadacca M, Conti L, Galluzzo S, Mitterhofer AP, Ferri GM, et al. Thrombosis in systemic lupus erythematosus: congenital and acquired risk factors. *Arthritis Rheum* 2005;53:452-9.
28. Askanase AD, Merrill JT. Measuring disease activity in SLE is an ongoing struggle. *Nat Rev Rheumatol* 2019;15:194-5.
29. Olsen FJ, Jorgensen PG, Mogelvang R, Jensen JS, Fritz-Hansen T, Bech J, et al. Predicting paroxysmal atrial fibrillation in cerebrovascular ischemia using tissue Doppler imaging and speckle tracking echocardiography. *J Stroke Cerebrovasc Dis* 2016;25:350-9.
30. Russo C, Jin Z, Homma S, Elkind MS, Rundek T, Yoshita M, et al. Subclinical left ventricular dysfunction and silent cerebrovascular disease: the Cardiovascular Abnormalities and Brain Lesions (CABL) study. *Circulation* 2013;128:1105-11.